Remarks

Amendments to the Claims

Claim 1 is amended to recite that the combination of *S. pyogenes* antigens includes a Spy0416 antigen. Claim 2 and page 26, lines 23-25 of the specification support this amendment. Claim 1 also is amended to recite that the recited combination of *S. pyogenes* antigens is in substantially pure form. Page 34, lines 9-12 of the specification supports this amendment.

Claim 2 is amended to recite that the Spy0416 antigen comprises the amino acid sequence SEQ ID NO:122. Page 27, lines 1-4 of the specification supports this amendment.

None of the amendments to the claims adds new matter.

Amendments to the Specification

The specification is amended to insert sequence identifiers on pages 3, 45, and 46 and to incorporate by reference the substitute sequence listing filed with this application. Neither of these amendments adds new matter.

Status of the Claims

The Office Action lists only claims 1, 4, 5, 10, and 14 as amended in the response filed September 22, 2008; however, claims 2 and 7 also were amended in that response. The present response amends claims 1 and 2 and cancels claims 10 and 14. Claims 1, 2, 4-9, 21, and 28 are now pending.

Elected Invention

On page 2, item 2 of the present Office Action, the Examiner acknowledges "Applicant's election of Group 1 (claims 1-14 and 23) and the combination of Spy 0269 (GAS 40, SEQ ID NO:1) and Spy0416 (GAS 57, SEQ ID NO:115) . . . ." This description of the elected invention is incorrect because Applicants did not elect an amino acid sequence for Spy0416. See page 2, item 3, where the Examiner confirms that "applicant did not inform the examiner SEQ ID NO for Spy0416."

In fact, the Restriction Requirement mailed on July 21, 2008 required election of only "a single disclosed SEQ ID NO from any group elected." Page 4. In response, Applicants provisionally elected SEQ ID NO:1, with traverse. If election of an amino acid sequence for Spy0416 is now required, Applicants provisionally elect SEQ ID NO:122 ***with traverse***. Claims 1, 2, 4-9, 21, and 28 read on the provisionally elected subject matter.

The Manual of Patent Examining Procedure states that "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." M.P.E.P. § 803. In this case, a search of any of the Spy0416 amino acid sequences disclosed in the specification would necessarily identify art relevant to each of the other disclosed sequences. A *prima facie* showing of a serious burden therefore has not been met. At most, election of a Spy0416 amino acid sequence should be a species requirement.

Objection to the Specification; Sequence Requirements

On page 3, the Examiner notes several inconsistencies in the sequence listing filed on January 19, 2006. A substitute sequence listing which addresses these inconsistencies accompanies this amendment. The substitute sequence listing contains only sequences disclosed in the application as filed and therefore does not contain any new matter.

The contents of the substitute sequence listing are identical to the contents of the sequence listing filed on January 19, 2006 except for the following:

- The amino acid sequence referred to in the specification on page 5, line 43 as "SEQ ID NO:3" is now SEQ ID NO:3 in the sequence listing. This amino acid sequence was inadvertently appended to SEQ ID NO:2 in the January 19, 2006 sequence listing, which caused each of the sequences in the original formal sequence listing to be off by one number (*e.g.*, SEQ ID NO:116 referred to in the specification was identified in the January 19, 2006 sequence listing as SEQ ID NO:115).
- SEQ ID NO:2 is now correctly presented as an amino acid sequence.
- The linker sequences disclosed on page 45 and oligonucleotides disclosed on page 46 of the specification are now included in the sequence listing as SEQ ID NOS:137-146.

Each of these corrections is fully supported by the specification, particularly by the informal sequence listing provided with the application as filed.

The Examiner also states on page 3 that "SEQ.ID.NOS 134 and 135 [in the January 19, 2006 sequence listing] are missing in the specification." SEQ ID NOS:134 and 135 in the January 19, 2006 are SEQ ID NOS:135 and 136 in the corrected sequence listing which

accompanies this amendment. Both SEQ ID NOS:135 and 136 are present in the informal sequence listing filed with the application. In addition, SEQ ID NO:136 (an example of the direct repeat sequences which flank the wild-type Spy0269 gene) is disclosed in the specification on page 10, lines 28-32.

Rejection Under 35 U.S.C. § 112 ¶ 2

Claims 1, 2, 4-10, and 14 are rejected under 35 U.S.C. § 112 ¶ 2 as indefinite. Claims 10 and 14 are canceled. Applicants respectfully traverse the rejection of claims 1, 2, and 4-9.

On page 4, the Office Action contends that:

> Claims 1-2 are vague and indefinite in the recitation of antibodies "Spy 0269" and "Spy0416" as the sole means of identifying the antigen. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define [a] completely distinct antigen.[1]

The terms "Spy0269" and "Spy0416" do not refer to antibodies and are not laboratory designations. They are art-accepted names for the *S. pyogenes* proteins recited in claim 1. For example, see the entries under GenBank Accession numbers Q9A1H3 and Q9A180, cited in the Office Action, which use the terminology "SPY0269" and "SPY0416," respectively.

The second paragraph of 35 U.S.C. § 112 states that:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[1] The Office Action cites Table 4 of Azcarate-Peril (*J. Dairy Sci. 92*, 870-86, 2009) as indicating that the term "Spy0269" can refer to different molecules. Table 4 does not support this contention. Table 4 lists *L. acidophilus* genes and, *inter alia*, the "COG category" to which each listed gene belongs. The "COG category" refers to the **c**luster of **o**rthologous **g**roups ([A], [M], [R], etc.) classification (see page 874, col. 2, ¶ 2 of Azcarate-Peril). Not all of the listed *L. acidophilus* genes fall into one of these categories. The authors apparently placed such genes into categories represented by other bacterial genes, and the LBA1690 gene was judged to be similar to SPy0269. "Spy0269" (or "Spy0269") is not, however, an alternative name for the LBA1690 gene.

It is well settled that a claim must "reasonably apprise those skilled in the art both of the utilization and scope of the invention." *Georgia-Pacific Corp. v. United States Plywood Corp.*, 258 F.2d 124, 136, 118 U.S.P.Q. 122, 130 (2d Cir. 1958), *cert. denied*, 358 U.S. 884 (1958). Claims 1, 2, and 4-9 meet this standard because they use terminology accepted and understood by those of skill in the art.

Even if, *arguendo*, this were not the case, the specification provides ample disclosure of which proteins the terms "Spy0269" and "Spy0416" refer. See *In re Cohn*: "No claim may be read apart from and independent of the supporting disclosure on which it is based." 438 F.2d 989, 993, 58 C.C.P.A. 996, 1001 (C.C.P.A. 1971). Spy0269 is identified, *e.g.*, on page 4, lines 24-28:

> GAS 40 corresponds to M1 GenBank accession numbers GI: 13621545 and GI: 15674449, to M3 GenBank accession number GI: 21909733, to M18 GenBank accession number GI: 19745402, and is also referred to as 'Spy0269' (M1), 'SpyM3_0197' (M3), 'SpyM18_0256' (M18) and 'prgA'. GAS 40 has also been identified as a putative surface exclusion protein. Amino acid and polynucleotide sequences of GAS 40 from an M1 strain are set forth below and in the sequence listing as SEQ ID NOS: 1 and 2.

Spy0416 is identified, *e.g.*, on page 26, lines 23-27:

> GAS 057 corresponds to M1 GenBank accession numbers GI: 13621655 and GI: 15674549, to M3 GenBank accession number GI: 21909834, to M18 GenBank accession number GI: 19745560 and is also referred to as 'Spy0416' (M1), 'SpyM3_0298' (M3), 'SpyM18_0464' (M18) and 'prtS'. GAS 057 has also been identified as a putative cell envelope proteinase. Amino acid and polynucleotide sequences of GAS 057 of an M1 strain are set forth in the sequence listing as SEQ ID NOS: 116 and 117.

Those of skill in the art would readily understand the scope of claims 1, 2, and 4-9. These claims are therefore definite. Please withdraw the rejection.

Rejections Under 35 U.S.C. § 102(b)

Claims 1, 2, 4-10, 14, 28, and 29 are rejected under 35 U.S.C. § 102(b) as anticipated by Biswas[2] and by Telford.[3] Claims 10, 14, and 29 are canceled. Applicants respectfully traverse the rejections of claims 1, 2, 4-9, and 28.

A reference cited under 35 U.S.C. § 102 must expressly or inherently describe each element set forth in the rejected claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Independent claim 1 as amended is directed to an immunogenic composition which comprises a combination of *S. pyogenes* antigens in substantially pure form. The combination consists of two to ten GAS antigens and includes a Spy0269 antigen and a Spy0416 antigen.[4]

The specification defines polypeptides of the invention which are in "substantially pure form" as polypeptides which are "substantially free from other GAS or host cell proteins." See Page 34, lines 9-12 of the specification. Neither Biswas nor Telford discloses a combination of purified *S. pyogenes* antigens "in substantially pure form" which consists of two to ten GAS antigens and which includes both a Spy0269 antigen and a Spy0416 antigen.

Biswas discloses a whole-cell extract, a cell wall preparation, and "supernatant proteins" of *S. pyogenes*. Page 7030, col. 2, ¶ 4. A suspension of *S. pyogenes* was lysed with a glass bead beater to prepare the whole-cell extract. *Id*. Cell wall preparations were obtained by digesting whole *S. pyogenes* cells with raffinose, mutanolysin, and lysozyme. *Id*. Proteins from the cell wall preparation were obtained by removing the cells by centrifugation and filtration,

[2] Biswas *et al.*, *Inf. Immun. 69*, 7029-38, 2001.

[3] Telford *et al.*, WO 2002/34771, May 2, 2002.

[4] The Office Action discusses coiled coil regions of M proteins in connection with both anticipation rejections. "Coiled-coil regions" of the Spy0269 antigen are recited in claims 4-9; however, M protein is a different protein. See page 28, line 5 to page 29, line 2 of the specification.

precipitating the proteins with trichloroacetic acid, washing the precipitated proteins with acetone, and resuspending the precipitated proteins in water. *Id.* None of these preparations comprises the recited combination of *S. pyogenes* proteins "in substantially pure form," *i.e.*, substantially free from other GAS proteins.

Telford is cited as disclosing *S. pyogenes* protein antigens, including Spy0269 and Spy0416, and immunogenic compositions comprising *S. pyogenes* protein antigens. Telford does not disclose an immunogenic composition comprising a combination of *S. pyogenes* antigens "in substantially pure form" (*i.e.*, substantially free from other GAS or host cell proteins) and including both Spy0269 and Spy0416.

Because neither Biswas nor Telford discloses each element of independent claim 1, neither of these references anticipates claim 1 or dependent claims 2, 4-9, and 28. Please withdraw the rejection.

Rejections Under 35 U.S.C. § 103(a)

The Office Action contains the following rejections under 35 U.S.C. § 103(a):

- claims 1 and 23 are rejected as obvious over Biswas or Telford;
- claims 1, 2, 4-10, 14, 28, and 29 are rejected as obvious over Dale[5] in view of Ferretti;[6] and
- claims 1 and 23 are rejected as obvious over Dale in view of Ferretti.

Claims 10, 14, and 29 are canceled. Applicants respectfully traverse the rejections of claims 1, 2, 4-9, 23, and 28.

[5] Dale, *Inf. Dis. Clinics North America 13*, 227-43, 1999.

[6] Ferretti *et al.*, *Proc. Natl. Acad. Sci. USA 98*, 4658-63, 2001.

Section 103(a) of 35 U.S.C. states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Obviousness under 35 U.S.C. § 103(a) is a question of law based on several factual inquiries:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966). The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. M.P.E.P., 8th ed., § 2142. In *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 407 (2007), the Supreme Court explained, "While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls." Moreover, it remains black letter law that obviousness requires at least a suggestion of all of the features in a claim. See *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003).

Independent claim 1 recites features of a combination of *S. pyogenes* (GAS) antigens in substantially pure form, consisting of two to 10 GAS antigens and including a Spy0269 antigen and a Spy0416 antigen. None of Biswas, Telford, or the cited combination of Dale and Ferretti teaches or suggests these features.

As discussed above in connection with the rejection under 35 U.S.C. § 102(b), Biswas discloses a whole-cell extract, a cell wall preparation, and "supernatant proteins" of *S. pyogenes* but does not teach an immunogenic composition comprising the recited combination of *S.*

pyogenes proteins "in substantially pure form," *i.e.*, substantially free from other GAS proteins. Nor does Biswas suggest such a composition. Biswas focuses on the *S. pyogenes* M protein, which is not a recited feature of claim 1, and its effect on virulence. Biswas does not disclose either Spy0269 or Spy0416 or suggest combining these antigens in an immunogenic composition.

Telford also does not suggest an immunogenic composition comprising a combination of *S. pyogenes* antigens "in substantially pure form" (*i.e.*, substantially free from other GAS or host cell proteins) and including both Spy0269 and Spy0416. Telford discloses many hundreds of antigens and does not point to the combination of Spy0269 and Spy0416.

Nor does the cited combination of Dale and Ferretti make the claimed immunogenic composition *prima facie* obvious. Dale is cited as teaching immunogenic compositions comprising a combination of antigens. Ferretti is cited as disclosing 13 predicted surface proteins containing LPXTG, including Spy0269 and Spy0416. Nothing in Ferretti, however, points to the particular combination recited in claim 1. In fact, even out of the 13 surface proteins disclosed in Ferretti, 78 combinations of two proteins can be made. As stated in *In re Kubin*, obviousness should not be found when one "merely throws metaphorical darts at a board filled with combinatorial prior art possibilities . . . ." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009). The Patent and Trademark Office cannot pick and choose isolated elements of a reference and piece them together using Applicants' specification as a template:

> [s]tatements [in a prior art reference] cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Kotzab, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Such an exercise is improper because it uses hindsight rather than considering the art from the viewpoint of the ordinary artisan at the time the present application was filed. *Id.* at 1369, 55 U.S.P.Q.2d at 1316.

In *KSR Int'l v. Teleflex Inc.*, the Supreme Court stated that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The Office Action does not articulate a reason why any of Biswas, Telford, or the combination of Dale and Ferretti would have motivated one of ordinary skill in the art to make an immunogenic composition comprising the specific combination of *S. pyogenes* antigens recited in independent claim 1. There is, therefore, no *prima facie* case that claim 1 or claims 2, 4-9, 23, and 28, which recite the features of claim 1, are obvious. Please withdraw the rejection.

Respectfully submitted,

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/Lisa M. Hemmendinger/

Date: August 7, 2009

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